UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/204,427	12/03/98	HADDADA H	8076.102USC1

HM12/0404

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EXAMINER	
LEE, G	
ART UNIT	**PAPER NUMBER**
1632	7

DATE MAILED: 04/04/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/204,427	Haddada et al.
Examiner	**Group Art Unit**
Gai (Jennifer) Mi Lee	1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1 and 3-8* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1 and 3-8* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachm nt(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 2 and 9-13 have been canceled in pre amendment filed 12/3/98.

Applicant's amendment filed December 13, 1999 has been entered.

Claims 1 and 3-8 are now pending.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250 words. It is important that the abstract not exceed 250 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

In the instant case, the abstract contains legal phraseology and is missing pronouns required for recitation in narrative form.

The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-References to Related Applications.
(c) Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
(e) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(i) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.
(l) Sequence Listing (see 37 CFR 1.821-1.825).

Proper headings in reference to the above contents would clarified the specification for examination.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in its recitation of "capable of" because it is unclear what factors are encompassed within the claim to make the homologous cassette deleted or not deleted. The metes and bounds of the claim cannot be determined.

Claim 1 is vague and indefinite in its recitation of "carry genetic information" because the specification does not define the sequences which make the defective adenovirus "carry genetic information" or not "carry genetic information" such that the metes and bounds of the claim can be determined.

Claim 1 is vague and indefinite in its recitation of "essential sequences" because the specification does not define those sequences which are "essential sequences" and which are not "essential sequences" needed for encapsidation. The metes and bounds of the claim cannot be determined.

Claims 1a, 1c and 6 are vague and indefinite in its recitation of " contains or containing", because the metes and bounds of the claim can not be readily established. In the absence of an express definition in the specification, it cannot be determined if "contains or containing" is narrow, open ended, or encompassing internal modifications. For examination, it will be given the broadest reasonable interpretation which is open ended. It is suggested that the term "comprises" or "consisting of" be recited instead.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

> has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1 and 3-8 are rejected under 35 U.S.C. 102(e) as being anticipated by Crystal et al (US Patent #6,013,638).

Crystal et al teach an adenovirus comprising deletions on the E1A, E1B and E3 regions for transfer of genes wherein genes include enhancement genes for local host defense and genes with antitumor properties, i.e. cytokines (IFN-gamma, IL-2, TNF-alpha, IFN-alpha, tumor suppressor proteins, IL-8 and IL-5) (column 3 and 4). Crystal et al further teach an expression cassette includes: the 5' inverted terminal repeat (ITR), origin of replication, encapsidation signal, and E1a enhancer (all from Ad5); the major later promoter and a copy of the tripartite leader sequence cDNA, the SV40 early mRNA polyadenylation signal and the remainder of the adenoviral vector genome (column 2, line 41-61). Crystal et al disclose that recombinant adenoviral DNA was then replicated and encapsidated into infectious virions which were screened by plaque purification and individual plaques were amplified in 293 cells (column 9). Thus, Crystal et al anticipates claims 1 and 3-8 of the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-8 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Rosenfeld et al. (1991) Science 252: 431-434 taken with Russell (1990) Immun. Today 11: 196-200; and Ramshaw et al. WO 8800971.

Rosenfeld discloses a replication deficient adenoviral vector containing an adenovirus major late promoter and an exogenous gene. Rosenfeld further discloses that the adenoviral vector has a deletion of a portion of E3 region, which is the region permitting encapsidation of the recombinant genome containing the exogenous gene, and further that the vector had a deletion in a portion of the viral E1a coding sequence, the deletion in E1a sequence impairing viral replication. Rosenfeld differs from the claims in that the reference fails to disclose insertion of cytokine genes, either singly or in multiples, into the E1a region. However, the secondary references, Russell and Ramshaw, cure the deficiency. Russell discloses the therapeutic potential of recombinant lymphokines against cancer and that to realize the therapeutic potential, alternative modes of delivery are needed. Russell discloses that tumor cell targeted lymphokine would optimize delivery (abstract). Russell discloses that lymphokines enhance the immune

response since Russell discloses that the cytokines can stimulate the local anti-tumor responses. Ramshaw discloses the combination of adenoviral vector having lymphokine genes such an interleukin or gamma-interferon inserted therein (abstract). It would have been obvious to one of ordinary skill in view of the teachings of Ramshaw to insert lymphokine genes into a replication defective adenoviral vector.

Russell provides the motivation to combine the references. Russell discloses the therapeutic potential of recombinant lymphokines against cancer and that to realize the therapeutic potential, alternative modes of delivery are needed. Russell discloses that tumor cell targeted lymphokine would optimize lymphokine delivery (abstract).

Regarding claim 3, the adenoviruse vector of Rosenfeld lacks the 5' end region downstream of the early promoter of the E1a region, see figure 1.

Regarding claim 4, Rosenfeld discloses placing an exogenous gene under the control of the adenovirus late promoter. It would have been obvious in view of the teachings of Ramshaw and Russell to place a single or multiple cytokine genes under the control of the late promoter since Rosenfeld discloses successful expression using the late promoter. Note that Ramshaw discloses using expressing cytokine genes from adenovirus vectors.

Regarding claim 5, it would have been obvious to one of ordinary skill to substitute a foreign (heterologous promoter) into the vector in order to control the expression of the cytokine genes. Russell clearly suggests the desirability of controlling cytokine secretion by the choice of gene promoter.

Regarding claim 6, Russell discloses using genes encoding singly or multiple cytokines for insertion into the desired replication deficient vector; see page 197, column 1, top paragraph. Note that the use of several promoters is obvious over the use of a single promoter since Russell discloses the desirability of controlling the level of cytokine secretion.

Regarding claim 7, the adenovirus of Rosenfeld is defective for reasons as set forth above.

Regarding claim 8, Rosenfeld discloses transfecting both epithelial cells as well as human embryonic kidney 293 cells, Russell discloses targeting tumor cells.

Accordingly, the modification of the vectors of Rosenfeld by substituting a gene or genes encoding a cytokine as suggested by Ramshaw and Russell in order to obtain a recombinant nucleic acid was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim 1 is rejected under 35 U.S.C. 103 as being unpatentable over Rosenfeld, Russell and Ramshaw as applied to claims 1 and 3-8 above, and further in view of Stratford-Perricaudet. Claims 1 and 3-8 were rejected for reasons as stated above. Rosenfeld, Russell and Ramshaw fail to teach an adenovirus vector lacking the transactivators E1A, E1B and E3 region of the adenovirus. Stratford-Perricaudet discloses that an adenovirus deleted for both regions E1 and

E3 would be able to carry up to 7 kb of foreign DNA. Thus, since it is well known in the art that the E1 region is composed of the Ela and E1b regions, it would have been obvious to one of ordinary skill to delete the entire E1 region in order to carry a larger heterologous gene, lacking evidence to the contrary. One of ordinary skill would have been motivated to modify the vector of Rosenfeld, Russell and Ramshaw by deleting the entire E1 region in order to obtain a vector containing more than one cytokine gene, lacking evidence to the contrary. Note that it is well accepted in the art that viral vectors have a limit as to the amount of heterologous DNA which can be usefully carried. It would have been obvious in view of the teachings of Russell, that vectors carrying multiple cytokine genes would be useful by deleting all nonessential portions of the vector DNA in order to make room for the genes encoding the desired cytokines.

Accordingly, the modification of the vector of Rosenfeld, Russell and Ramshaw by deleting the E1a and E1b region as suggested by Stratford-Perricaudet in order to obtain a recombinant nucleic acid was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Acknowledgment is made of applicant having presented argument at Paper No. 3, pages 3-6 of the paper filed 3 December 1998, directed toward the Final Office action in US Serial

Number 08/619,157, mailed 3 January 1998. Applicant's arguments filed December 13, 1999 have been fully considered but they are not persuasive towards the withdrawal of the previous rejection of claims in the parent application under 35 U.S.C. 103 (a). To the extent that applicants arguments apply to the instant application, they will be addressed.

Acknowledgment is made of applicant having filed a Declaration under 37 CFR 1.132 by Majid Mehtali, Ph.D., signed 18 November 1998. The declaration of Dr. Mehtali has been considered and is addressed, below.

Dr. Mehtali states that no prior references for selection by a skilled scientist to treat cancerous tumors as disclosed by Russell. Dr. Mehtali states that from the teachings of Russell, a skilled scientist would glean that this reference teaches against using a defective recombinant vector due to the problems associated with access by defective vectors to poorly vascularized tumor region and that the only guidance given to the skilled scientist in Russell was the recognition that competent viral vectors should be chosen since they could facilitate infection of a higher proportion of tumor cells.

The statements by Dr. Mehtali concerning Russell are unconvincing, this reference clearly shows the interest in the art in genetic cytokine therapies and viral vector-mediated delivery was clearly in the forefront. Russell merely suggest to make viral vectors comprising cytokine coding regions to develop effective cancer therapeutics. The claims are directed to rejection of the products not the implied use or methods of the product.

Dr. Mehtali further states that the skilled scientist would not use defective vectors to accomplish the teachings of Ramshaw et al. Dr. Mehtali states that Ramshaw disclose a variety of vector systems such as poxvirus, vaccine virus, herpes virus, adenovirus or bacteria in which a nucleic acid encoding a lymphokine is also disclosed for enhancement of the immune response to the antigenic polypeptide that is expressed.

The statements concerning Ramshaw et al are also unconvincing. Ramshaw et al clearly demonstrates that adenoviral vectors expressing cytokines were explicitly taught in the prior art. It is also noted that the insertion of additional coding sequences would reinforce the need for adenoviral vectors with the entire E1 and E3 regions deleted to provide more space for the extra insertions.

Dr. Mehtali further states that a skilled scientist would not be guided to remove the E1a and E1b regions from the teachings of Rosenfeld et al and that this reference relates to defective gene therapy and not to treat tumors which is discussed.

The statements concerning Rosenfeld et al are also unconvincing. Rosenfeld et al disclose a replication deficient adenoviral vector containing an adenovirus major late promoter and an exogenous gene with further deletion of a portion of E3 region and deletion in a portion of viral E1a coding sequence, thus, the deletion of E1a sequence impairs viral replication. However, this limitation of removing the E1a and E1b region is not recited in the claims. Rather, claim 1 recites that the E1a and E1b transactivators are lacking. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the

claims. *In re Van Guens*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Since an active E1a transcript is required for expression of E1b protein, this limitation of claim 1 is met in Rosenfeld et al.

Dr. Mehtali further states that a skilled scientist would not know from the reading of Stratford-Perricaudet et al if an adenoviral vector can be use the treat cancerous tumors because Stratford-Perricaudet et al teach replacement gene therapy and not to cancer therapy (point 11).

The statements concerning Stratford-Perricaudet are also unconvincing. Stratford-Perricaudet discloses that an adenovirus deleted for both regions E1 and E3 would be able to carry up to 7 kb of foreign DNA which would increase the available space for a heterologous insert was well known in the art. Regardless of whether one would have been motivated to delete the entire E3 region because of immunogenic properties, the prior art still suggests deleting all of the regions. This reference also discloses that adenovirus was commonly used as a cloning vector, thus the statements by Dr. Mehtali to gene therapy and not to cancer therapy (as further stated in point 11 of the declaration to cancer therapy) have no patentable weight because the claims are directed to a product.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gai (Jennifer) Mi Lee, whose telephone number is 703-306-5881. The examiner can normally be reached on Monday-Thursday from 8:30 to 5:00 (EST). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on 703-308-2035. The FAX phone numbers for group 1600 are 703-308-4242 and 703-305-3014.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Gai (Jennifer) Lee
Patent Examiner
Art Unit 1600

Karen M. Hauda
Karen M. Hauda
Patent Examiner